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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 08/927,939 | 09/11/1997 | DAVID J. GRAINGER | 295.022US1 | 9003 |

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| EXAMINER |
|---|
| MURPHY, JOSEPH F |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | 35 |

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/927,939 | GRAINGER ET AL. | |
| | Examiner | Art Unit | |
| | Joseph F Murphy | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,4,6-11,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 6-11* is/are rejected.

7)☒ Claim(s) *42 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Formal Matters*

Claims 1 and 42 were amended in Paper No. 32, 5/31/2002. Claims 1, 3-4, 6-11, 42-43 are pending and under consideration.

### *Response to Amendment and Arguments*

The rejection of claims 1, 3-4 and 6-10 under 35 U.S.C. 102(b) as being anticipated by WO 9520973 has been withdrawn.

### *Claim Rejections - 35 USC § 112 first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4, 6-11 stand rejected under 35 USC § 112, first paragraph because the specification, while being enabling for peptides of SEQ ID NO: 85, and cyclic reverse sequence derivatives with the sequence CRD-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln-Cys, does not reasonably provide enablement for a variant or a derivative of SEQ ID NO: 84 which inhibits the activity of at least one native chemokine, for reasons of records set forth in Paper No. 10, 4/7/1999 and Paper No. 14, 11/12/1999 and 3/5/2001.

The claims are drawn to variants and derivatives of peptides which inhibit the activity of at least one native chemokine. The rejection of record set forth that since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any

experimentation is necessary, but whether, if experimentation is necessary, it is undue. The unpredictability of the protein art as relates to making substitutions that do not alter the function of the polypeptide, and the sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Mikayama et al. (1993) which teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. The Bowie et al. reference further teaches that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306).

Applicant argues that the claims are directed to peptides of 30 residues or less, and that thus the amino acid substitutions will have unpredictable effects on protein function. However, this functional limitation is overbroad because it encompasses the activity of any chemokine. The skilled artisan would thus need to construct all the possible variants and substitutions of the claimed polypeptides, and screen for activity by examining the inhibition of all possible chemokines, this would require undue experimentation. However, Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass peptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make the claimed peptides, since the skilled artisan would have to first make the peptide variants, then test for function. Since the claims as written set forth an overly broad functional limitation for the encompassed peptides the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant further argues that the specification demonstrates that substitutions do not alter peptide function. However, Applicant has not demonstrated all possible substitutions, nor has Applicant set forth the conserved regions that are critical to the structure and function of the peptides as broadly claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function, thus the

skilled artisan would have to make the peptide variants then test for function, against all possible chemokines.

Based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and the Mikayama et al. and Voet et al. references which demonstrates that the change of a single amino acid can radically alter protein function, and absent sufficient evidence to the contrary it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 1, 3-4, 6-11 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of records set forth in Paper No. 10, 4/7/1999 and Paper No. 14, 11/12/1999 and 3/5/2001. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to variants and derivatives of peptides that inhibit the activity of at least one native chemokine. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural

differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, peptide sequence as set forth in SEQ ID NO: 84 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant further argues that the detailed structure of the peptides was envisioned as shown in Example 2. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides used in the claimed method. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to

function. Additionally, functional limitation is overbroad because it encompasses the activity of any chemokine. The skilled artisan would thus need to construct all the possible variants and substitutions of the claimed polypeptides, and screen for activity by examining the inhibition of all possible chemokines. Since the skilled artisan would have to determine by trial and error the peptides that meet the limitations of the claims, the genus as claimed in not described.

***Conclusion***

Claims 1, 3-4, 6-11 are rejected.

Claims 42 and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
September 26, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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